Blood Sub[illegible]tes
Baxter Healthcare Co[illegible]tion
Route 120 & Wilson R.
Round Lake, Illinois 60073-049[illegible]
847.270.5300
Fax: 847.270.5306

Baxter

May 29, 1997

0769 97 JUN -3 AM 10:42

Docket Number 95S-0158
Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Dr. rm. 1-23
Rockville, MD 20857

RE: Investigational New Drug Application #6859

Dear Sir/Madam:

In accordance with 21 CFR §312.54 we are enclosing a copy of the information that has been publicly disclosed by the Institutional Review Board (IRB) at Oregon Health Sciences University, Portland, OR, concerning research involving an exception to informed consent. This includes an advertisement that ran in the following local newspapers on the following dates: *The Oregonian* on April 30 and May 4; the *Vancouver Columbian* on May 2 and May 4; and the *Scanner* on May 7 (Attachment 1), and a Community Consult letter that was sent out to select community members determined by the IRB (Attachment 2). A protocol synopsis was sent to individuals who requested additional information on the study (Attachment 3), and a copy of 21 CFR §50.24 was sent to individuals who requested additional information on the regulations regarding waiver of informed consent (Attachment 4). In accordance with 21 CFR §312.54, this information is also being submitted to the IND file.

Based on information received from the clinical site, the investigator and IRB achieved community consultation by soliciting oral comments from the community via an advertisement (Attachment 1), and by soliciting written, electronic, and oral comments from various community members via a Community Consult letter (Attachment 2). A dedicated telephone line was established for callers. Recorded messages of the community inquiries were sent to the study coordinator. A dedicated telephone line was established for callers. Recorded messages of the community inquiries were sent to the study coordinator. Individuals requesting additional information about the study were sent a copy of the protocol synopsis (Attachment 3), and individuals requesting additional information on the regulations regarding waiver of informed consent were sent a copy of 21 CFR §50.24 (Attachment 4).

95S-0158

SUP3

If there are any questions concerning this information, please contact me at (847)270-5313.

Sincerely,

Maulik Nanavaty, Ph.D.
Director Regulatory Affairs
Blood Substitutes Program

Attachment 1

An important message from the physicians and emergency medical staff at Oregon Health Sciences University Hospital

Oregon Health Sciences University's fundamental aim is to improve the health of all Oregonians. Through our three-part mission of healing, teaching and scientific investigation, OHSU educates health professionals and biomedical researchers in a variety of fields, and undertakes the functions of patient care, community service and biomedical research.

As part of our research function, we have been selected to be one of 40 trauma centers in the United States to study a new treatment that has the potential to save the lives of severely injured trauma patients who are in shock due to blood loss.

The treatment is an oxygen-carrying agent known as Diaspirin Cross-Linked Hemoglobin, derived from human blood. DCLHb has been tested in clinical trials across the country with more than 350 patients, and its safety is well-documented. It has been shown to increase blood pressure and decrease the need for blood transfusions in a number of procedures.

A small number of patients (20-30) will be selected at Oregon Health Sciences University, according to strict study criteria. These patients will be men and women 18 years of age or older who are suffering from serious blood loss and are at the greatest risk of dying. Study patients will receive the hemoglobin agent in addition to standard treatments.

The study is made possible in part by new guidelines from the Food and Drug Administration. The guidelines allow physicians, under rigorous control, to administer new, potentially life-saving treatments to patients too ill to give their consent. Under the guidelines, patients with life-threatening conditions who are unable to sign a consent, or who do not have a family member who can sign for them, still may be eligible to receive promising trial therapies in addition to standard treatments.

Participation in this study is confidential. Every effort to obtain consent from a family member or legally authorized representative will be made. If informed consent to participate in this study cannot be obtained during the 30-minute critical time period after a patient is admitted to the hospital, the patient may be entered into the study under the "exception from informed consent" authorized by the FDA.

Traumatic injury is the leading cause of death among Americans ages 1 through 45 years, and affects nearly 2 million people every year. The results of this study will help advance knowledge about the treatment of severe traumatic injuries.

A hotline has been established at (503) 494-1400 to respond to questions about this study.

This message is provided in Accordance with the U.S. Food and Drug Administration (FDA) regulation, effective November 1, 1996, "Exception from informed consent requirements for emergency research" (21 CFR 50.24).

This study has been approved by the Oregon Health Sciences University Institutional Review Board.

OHSU

Where Healing, Teaching and Discovery Come Together

OHSU OREGON HEALTH SCIENCES UNIVERSITY

Attachment 2

Providence St. Vincent Medical Center
Quality Management
9205 SW Barnes Rd.
Portland, OR 97225

April 26, 1997

To Whom It May Concern:

We would appreciate your comments on the following study.

The Oregon Health Sciences University Department of Emergency Medicine, in collaboration with the Trauma Service, will be starting a new study involving trauma patients in shock due to blood loss. The study is made possible in part by new guidelines from the Food and Drug Administration. It involves the enrollment of patients with life-threatening conditions in clinical research studies. The guidelines allow physicians under rigorous control to administer new, potentially life-saving treatment to patients too ill to give their consent.

Under the new guidelines, patients with life-threatening conditions who are unable to sign a consent or who do not have a family member who can sign for them, may still be eligible to receive promising trial therapies in addition to standard treatments. We will still make every effort to obtain standard consent prior to treatment, and the new guidelines will apply only in extreme circumstances when prompt medical attention is crucial and conventional therapy may be inadequate.

Traumatic injury is the leading cause of death among Americans ages 1 through 45 and affects nearly 2 million people every year. The results of this study will help advance knowledge about treatment of severe traumatic injuries.

OHSU expects to enroll approximately 25 patients into the study. Participants will be those who by virtue of their injuries will have at least a 40% to 50% risk of dying with conventional treatments alone. Half will receive the study agent in addition to standard therapy, the other half will receive only the standard treatments. This study will be conducted at a number of medical centers and it will involve approximately 850 trauma patients across the country. The OHSU Institutional Review Board, which reviews all research that involves human subjects, has approved this study.

The agent has been tested in medical centers across the country and its safety is well documented. It is an oxygen-carrying agent that is made from screened human blood. It has been shown to increase blood pressure and decrease the need for blood transfusions in a number of procedures including orthopedic surgery, vascular surgery and gastrointestinal surgery. More than 350 patients have received the drug in these national studies.

We welcome your comments regarding this study. A hotline has been established to respond to questions. Please call (503) 494-1400 or write to Oregon Health Sciences University, Attn. Patrick Brunett, MD., Principal Investigator, UHN 52, 3181 SW Sam Jackson Park Rd., Portland, OR 97201-3098. You may also respond by E-mail to mcdevitt@ohsu.edu or brunettp@ohsu.edu.

Sincerely,

Colleen McDevitt
Senior Research Assistant

Patrick Brunett, MD
Principal Investigator

Attachment 3

03 October 1996

Protocol Synopsis

"The Efficacy Trial of Diaspirin Cross-linked Hemoglobin (DCLHb™) in the Treatment of Severe Traumatic Hemorrhagic Shock"

Introduction

Death from trauma frequently results from shock that is refractory to resuscitation efforts. These efforts typically involve rapid infusions of large volumes of crystalloid solutions. This standard of therapy has been brought into question by recent clinical studies utilizing small volumes of hypertonic saline-Dextran solution (Mattox et al. 1991, Ann Surg 213:482-91), or no volume replacement until definitive surgical treatment (Bickell et al. 1994, N Eng J Med 331:1105-1109).

Trauma-related mortality has been correlated with the magnitude of base deficit. According to Siegel et al. (Arch Surg 1990, 125:498-508), a base deficit of 11.8 mmol/L predicts a mortality of 50% in trauma patients presenting with pelvic fractures or blunt liver trauma. Rutherford et al. (J Trauma 1992, 33:417-423) reported a mortality rate over 40% in trauma patients with base deficits in excess of 15 mmol/L. This study of 3791 trauma patients also showed a sharp, corresponding rise in mortality rates from 20% to 40% over the base deficit range of 10 to 15 mmol/L.

The above findings suggest that the current practice of restoring blood pressure through large volume crystalloid infusion may be suboptimal in traumatic hemorrhagic shock patients. These traumatic shock patients, especially those with large base deficits, are at greatest risk, and warrant being studied with a controlled clinical trial with a low volume pressor/perfusion agent such as DCLHb.

Initial DCLHb Hemorrhagic Shock Trial

The initial prospective, randomized, escalating dose clinical trial of DCLHb in hemorrhagic shock studied the infusion of normal saline (NS) or DCLHb in class II-IV shock patients within four hours of the shock episode. The trial was divided into three dose ranges, 50 mL (71 mg/kg), 100 mL (143 mg/kg), and 200 mL (286 mg/kg). Each dose included approximately 40 patients (20 NS, 20 DCLHb). Patient enrollment for this clinical trial was completed in May 1995 with a total population of 139 patients, 71 (51%) of whom received DCLHb.

No increase in the rate of complications or toxicities in patients who received DCLHb were observed during the trial. Specifically, renal insufficiency and failure were not more common in DCLHb-treated patients. Overall mortality rates, complications and adverse event rates did not differ in the DCLHb and control groups. These findings, and findings from several other DCLHb trials at different doses (750-1200 mLs), suggest that DCLHb infusion will have a favorable risk/benefit profile in severely injured patients.

Study Design

This will be a multicenter, randomized, placebo-controlled (normal saline) study. Inclusion in this protocol will not interfere with the provision of any standard trauma therapy.

Primary Clinical Benefit Endpoint

- Clinically and statistically significant reduction in 28 day mortality.

Secondary Clinical Benefit Endpoint

- Clinically and statistically significant reduction in morbidity.
- Clinically and statistically significant reduction in 48 hour mortality.
- Clinically and statistically significant reduction in 24 hour lactate levels.

Patient Population

The study population will be a small subset of trauma patients with persistent, severe, hypoperfusion despite aggressive pre-hospital therapy. To properly investigate the mortality and morbidity outcomes in this protocol, 500 to 1000 mL DCLHb or the saline control will begin being infused no later than 30 minutes after meeting the entry criteria and within 60 minutes of presentation to the emergency department in approximately 850 patients meeting the following inclusion criteria:

1. Males or females 18 years of age or older
2. Evidence of hemorrhage
3. Tissue hypoxia and cellular hypoperfusion shown by:
   - Systolic blood pressure ≤ 90 and pulse ≥ 120 or,
   - Systolic blood pressure ≤ 90 and pulse < 60 with a pre-terminal rhythm (junctional or idioventricular) or,
   - Base deficit of 15 mmol/L or worse

Patients will be excluded from the study by the following exclusion criteria:

1. Age <18 years
2. Known pregnancy
3. Pulseless traumatic arrest during hospitalization
4. Imminent death precludes resuscitation efforts
5. Isolated head trauma, penetrating or blunt
6. Combined multisystem and head trauma with clinical findings consistent with significant mass effect (e.g., severe coma, lateralizing signs, posturing, or pupillary dilatation secondary to uncal herniation)
7. Hospitalization >60 minutes prior to infusion
8. Known objection to the use of blood, blood products
9. Known injury time >4 hours prior to infusion

Statistical Approach

Approximately 850 patients will be needed to show a 25% reduction in mortality (i.e., from 40% to 30%). A Cox proportional hazards model will be used to determine the impact of DCLHb on mortality while adjusting for demographic and pre-treatment covariables documented as predictors of mortality. Interim monitoring will occur at 10%, 25%, 50%, 75% and the final analysis at 100% enrollment of the 850 patients.

Safety Monitoring

An independent Data Monitoring Committee (members not affiliated with Baxter Healthcare) will be established by the sponsor. Ongoing safety monitoring will be performed by this committee during the enrollment of study patients. If major safety concerns arise, the study can be amended or put on hold until these concerns are addressed.

Informed Consent

The consent procedures followed in the protocol will follow 21 CFR 50.24 "Exception from informed consent requirements for emergency research". These regulations will be utilized based on the favorable risk/benefit profile of DCLHb and the frequent lack of feasibility in obtaining prospective informed consent in this patient population.

Attachment 4

Sec. 50.24 Exception from informed consent requirements for emergency research.

(a) The IRB responsible for the review, approval, and continuing review of the clinical investigation described in this section may approve that investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following:

(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

(2) Obtaining informed consent is not feasible because:

(i) The subjects will not be able to give their informed consent as a result of their medical condition;

(ii) The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and

(iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

(3) Participation in the research holds out the prospect of direct benefit to the subjects because:

(i) Subjects are facing a life-threatening situation that necessitates intervention;

(ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and

(iii) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

(4) The clinical investigation could not practicably be carried out without the waiver.

(5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with Sec. 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.

(7) Additional protections of the rights and welfare of the subjects will be provided, including, at least:

(i) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;

(ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;

(iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;

(iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and

(v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

(b) The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.

(c) The IRB determinations required by paragraph (a) of this section and the documentation required by paragraph (e) of this section are to be retained by the IRB for at least 3 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by FDA in accordance with Sec. 56.115(b) of this chapter.

(d) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under Secs. 312.30 or 812.35 of this chapter.

(e) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

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